### Figure 1A

### I. Diamino Carboxylic acid-Based Cationic Lipid

### II. Quarternary Diamino Carboxylicacid-Based Cationic Lipid

### Lipophilic Group

Head Group

n = 1-3,  $n_1 = 2-5$ 

Head Group

Linker

 $R_1 = C12-C22$  saturated or unsaturated (1-4 double bonds) alkyl chain.

R<sub>2</sub>,R<sub>3</sub> = H, acyl, alkyl, carboxamidine, N-alkyl (aryl, acyl, PEG) substituted carboxamidine, PEG, or combination thereof.

Alk = methyl, hydroxyethyl or combination thereof.

### III. Guanidinium-Based Cationic Lipid

### IV. Mono Amino-Based Cationic Lipid -NHR<sub>2</sub> Head Group

 $R_2=H,$  carboxamidine, N-alkyl (aryl, acyl, PEG) substituted carboxamidine, PEG

$$R_2 = H$$
, acyl, alkyl, PEG

V. Polyamine-Based Cationic Lipid

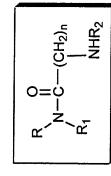
R<sub>2</sub>=R<sub>3</sub>=H R<sub>2</sub>=PEG, R<sub>3</sub>=H R<sub>2</sub>=H, R<sub>3</sub>=PEG

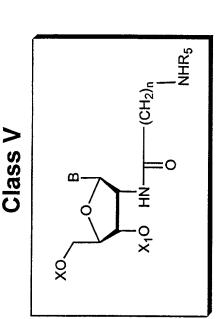
Linker Lipophilic Group

 $R_1 = R_3 = H$ , or

### Figure 1B: Mono Amino-Based Cationic Lipid

### Class IV





R,R<sub>1</sub> = C12-C22 saturated or unsaturated (1-4 double bonds) alkyl chain.

$$n = 2.6$$

$$R_2 = H, \qquad \text{Or} \qquad$$

PEG: or PEG 2000 carbonyl, PEG 5000

carbonyl

methoxypolyoxyethylene carbonyl (Ave. Mol. Wt. = 2000 or 5000)  $R_3$ = H,  $PO_3H_2$ , PEG  $R_4$  = OH,  $NH_2$ , =0, O-PEG  $R_5$  = H, carboxamidine

X=R, X1=R1, X=R1, X1=R X=PEG, X<sub>1</sub>=H X= X1=R, R1

 carbamate CO-PEG2000 - amide COOPEG

 $X=H, X_1=PEG$  B= nucleic acid base (modified or unmodified) or H

### Figure 1C

General formula:

R = saturated or unsaturated (1-4 double bonds) alkyl chains (12-22C) R<sub>1</sub> = TREN, N,N'-di-carboxamidine TREN, lysyl, arginyl, ornithyl, -NHCOR -NHCOR

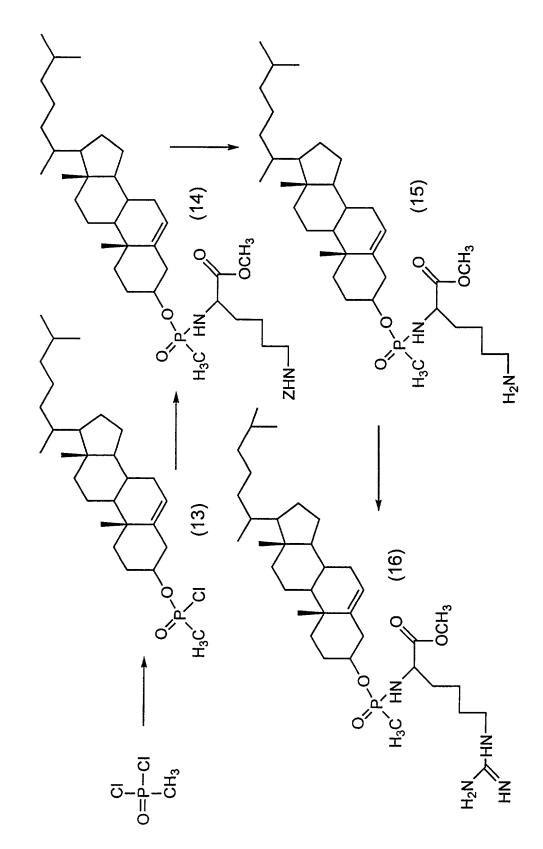
homoarginyl, histidyl, aminopropylimidazole, spermine carboxylic acid.

-COR<sub>1</sub>

Figure 2

## Figure 3: Synthesis of DS 46596 (12)

# Figure 4: Synthesis of PH 55933 (15), 55938 (16)



## Figure 5: Synthesis of PH 55939 (17)

# Figure 6: Synthesis of PH 55941 (18), 55942 (19)

## Figure 7: Synthesis of PH55943 (20)

## Figure 8: Synthesis of PH 55945 (21)

# Figure 9:VITAMIN B<sub>6</sub> and $\beta$ -Ala-BASED CATIONIC LIPIDS

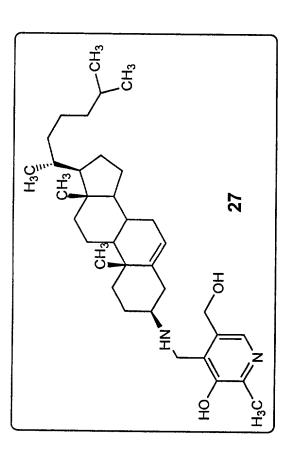
1,4-cyclohexadiene; iv) a: pyridoxal/EtOH, b: NaBH4; v) 1H-pyrazole-1-carboxamidine/THF-MeOH REAGENTS AND CONDITIONS: i) N-hydroxysuccinimide, DCC; ii) HNR2, Et3N; iii) 10% Pd/C,

### Figure 10

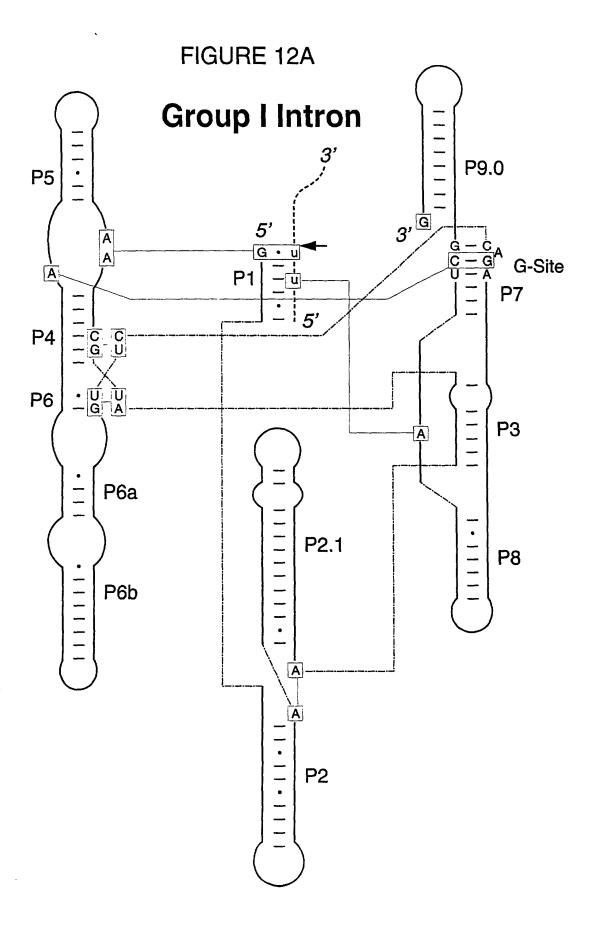
Reagents and conditions: i) N-Fmoc-b-Ala, EEDQ/MeOH; ii) C<sub>15</sub>H<sub>31</sub>COCI/Py; iii) morpholine/CH<sub>2</sub>Cl<sub>2</sub>; iv) 1*H*-pyrazole-1-carboxamidine/THF-MeOH

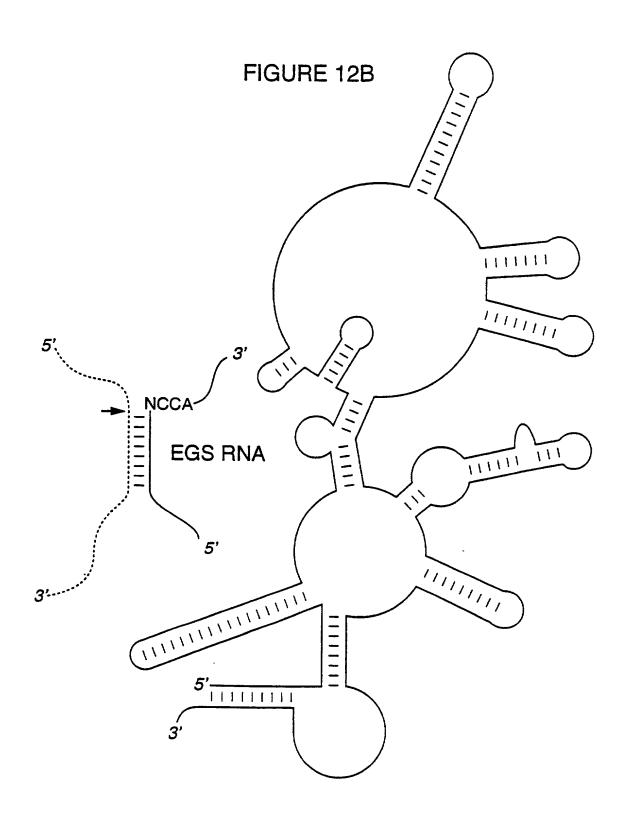
# Figure 11: VITAMIN B<sub>6</sub> -CHOLESTEROL CONJUGATE

Cholesteryl chloride



REAGENTS AND CONDITIONS: i) NH<sub>3</sub>/MEOH; ii) reductive amination of pyridoxal





### FIGURE 12C

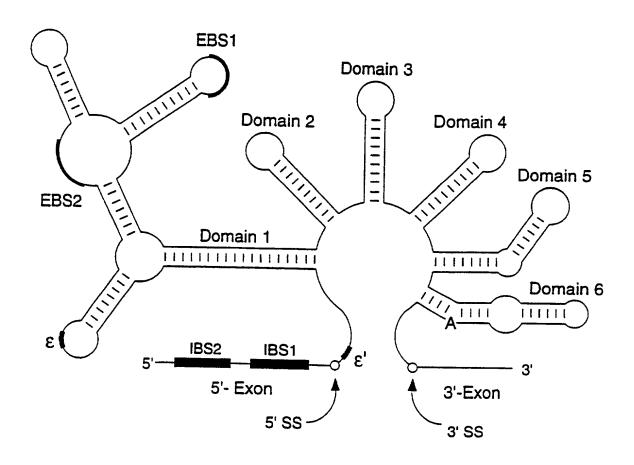
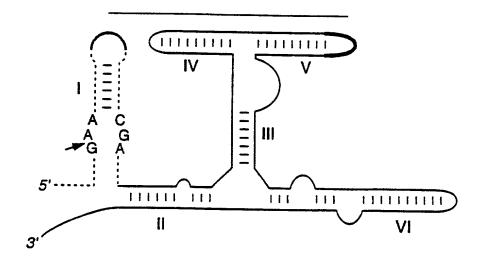
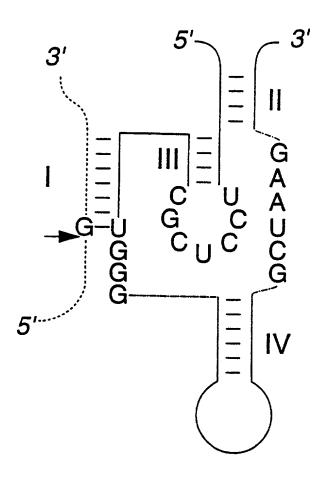


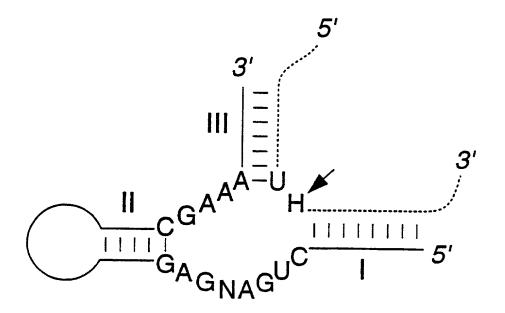
Figure 12D



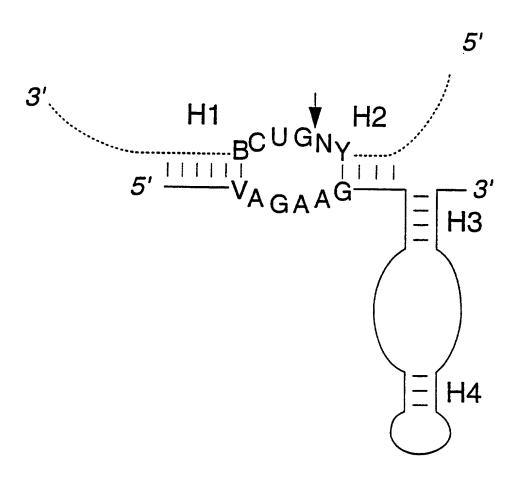
### FIGURE 12E



### FIGURE 12F



### FIGURE 12G



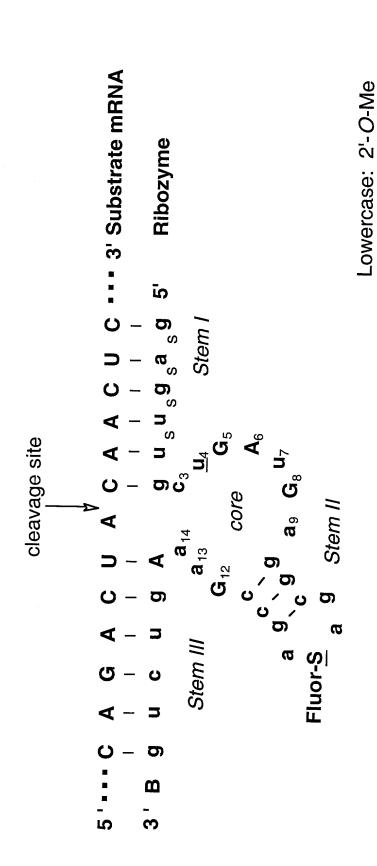


Figure 13

Uppercase: ribonucleotide B: inverted deoxy abasic s: phosphorothioate S: c6 dT amino linker

Figure 14

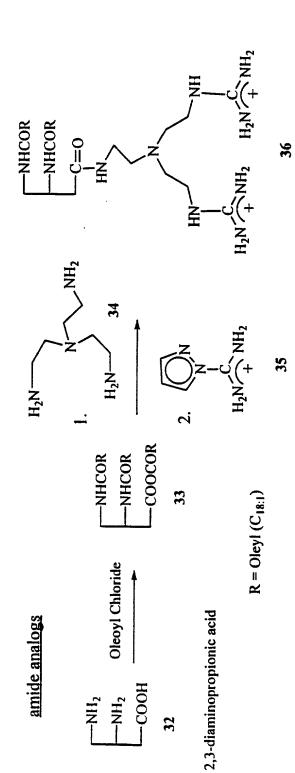


Figure 15: Concentration of Intact Ribozyme after Intravenous Administration of EPC: CHOL: DOTAP: DSPE-PEG 2000 20 Liposome Encapsulated Ribozyme 10 104 1000 Intact Ribozyme (ng/mL plasma)

25

Figure 16: Inhibition of IMPDH-2 mRNA Expression in Jurkat Cells Treated for 24 h with IMPDH antisense molecule + 5 μg/ml Formulation ID No. 345

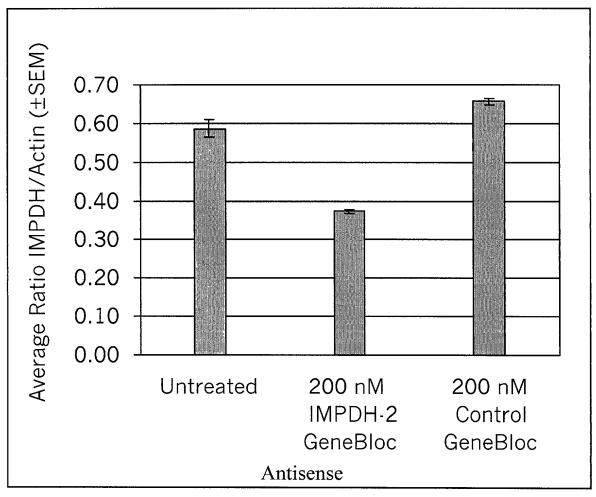


Figure 17: Inhibition of IMPDH-2 mRNA Expression in Jurkat Cells Treated for 24 h with IMPDH Antisense molecules+ Formuation ID NO: 323

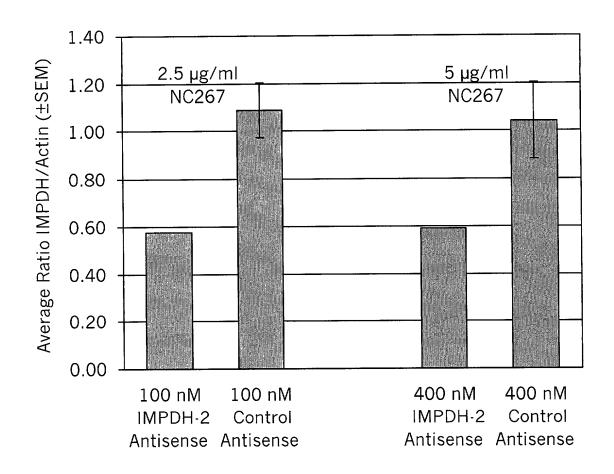


Figure 18: Inhibition of IMPDH-2 mRNA Expression in Jurkat Cells Treated for 24 h with IMPDH antisense molecules + Formulation ID NO: 333

